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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,398	08/03/2000	ABDESSATAR CHTOUROU	065691/0193	9759

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1653	9

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,398	Applicant(s) CHTOUROU ET AL.	
	Examiner Abdel A. Mohamed	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

ACKNOWLEDGMENT OF AMENDMENT, RESPONSE AND STATUS OF THE CLAIMS

1. The amendment and remarks filed 5/20/02 are acknowledged, entered and considered. In view of Applicant's request claims 1-23 have been canceled and claims 24-51 have been added. Thus, claims 24-51 are now pending in the application. The objection to the title, abstract, trademarks and improper multiple dependent claims; and the rejections under 35 U.S.C. 112, first paragraph and 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment, remarks and cancellation of claims filed 5/20/02. However, the objection to the arrangement of the specification and the rejection under 35 U.S.C. 103(a) over the prior art of record are maintained.

2. The specification remain objected because there are no Headings disclosed in the disclosure and the following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicant's use.

ARRANGEMENT OF THE SPECIFICATION

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-References to Related Applications.

© Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).

(e) Background of the Invention.

1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(I) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821-1.825).

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

It is noted that Applicant has canceled claims 1-23 and instead submitted new claims 24-51 which have been amended to correct multiple dependency and have been rephrased to read more clearly and conform to current standard of USPTO practice. Thus, the same 103(a) rejection over the prior art of record is applied to newly submitted claims 24-51.

Claims 24-51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed. Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657).

WO 96/00237 teaches a method of virus-filtering a solution that contains at least one macromolecule, particularly factor VIII which may be native or recombinant, wherein the salt content of the solution lies in the range of from about 0.2 M up to saturation of the solution with the salt concerned (See e.g., abstract, page 5, lines 14 to 24 and claim 1). On page 7, lines 30 to

page 9, lines 27, the reference clearly teaches the use of various filters which are readily available commercially such as Planova™ 15 filter for virus filtration having a porosity as low as 15 nm for the intended purpose of reducing the content of very small non-enveloped viruses, such as parvoviruse, polio virus, hepatitis virus, ect. Thus, the primary reference clearly teaches a method for obtaining a variety of safe solution of the plasma protein complex such as FVIII by a filtration step using a filter with a porosity of 15 nm.

The primary reference of WO 96/00237 differs from claims 24-51 in not using chaotropic ions such as calcium for dissociation purpose and the purification of the cryoprecipitate fraction of the plasma by ion exchange chromatography. However, Josic et al. teach the purification of FVIII and vWF from human plasma by anion-exchange chromatography, wherein the purification is carried out by a combination of precipitation and chromatographic procedures. After precipitation, the first step in virus inactivation is achieved through the effect of a non-ionic detergent such as Tween 80, and as solvent such as TnBp (i.e., inactivated by solvent/detergent treatment as claimed in claim 41). By anion-exchange chromatography, a highly enriched product consisting of a complex formed by FVIII and vWF is isolated. The second step in virus inactivation is conducted with the addition of stabilizers, pasteurization and subsequent removal by ion-exchange chromatography. The resulting complex of FVIII and vWF are dissociated by adding calcium ions and subsequently both glycoproteins from the complex are separated from one another by further anion-exchange chromatography (See e.g. abstract, pages 183-184 and

Figure 1). Thus, clearly teaching the separation of FVIII and vWF using treatment by calcium ions after purification of the FVIII-vWF plasma complex using chromatographic techniques.

Further, Grandgeorge et al (U.S. Patent No. 5,71,195) teaches a method for purifying FVIII from cryoprecipitate, enabling chromatographic yields of more than 90% to be achieved by dissolving FVIII and subjecting to viral inactivation with solvent/detergent and further subjecting to chromatography on a weak anion-exchange column which is hydrophilic in nature and FVIII is then eluted with a dissociating buffer (See e.g. abstract and summary of the invention). Furthermore, Farb et al discloses a multi-step process for separating FVIII from plasma in which at least one of the steps require the adsorption of FVIII on a hydrophilic interaction matrix (See e.g. summary of the invention). Moreover, as acknowledged on page 2, lines 23-32 in the instant specification, the elimination of vWF proteins (that is, implicitly, high molecular weight vWF, and therefore, implicitly, free of high molecular weight vWF). Thus in view of this and in view of the teachings of the secondary references, one of ordinary skill in the art could have envisaged filtering the solution of dissociated FVIII/vWF which is obtained as a product which is free of virus and devoid of vWF by combining a filtration and dissociation steps using a filter with a porosity of 15 nm. Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary references to the primary reference because such features are known or suggested in the art, as seen in the secondary references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claim 51, the claim is in product-by-process format and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, In re Best, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to the Applicants, In re Fitzgerald, 205 USPQ 594.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ a method for obtaining a virus free solution of the plasma protein complex of FVIII, said solution essentially being free of high molecular weight vWF and obtained from a solution containing high molecular weight FVIII-vWF complexes, said method combining a dissociation step and a filtration step using a filter with a porosity of 15 nm., absence of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

4. Applicant's arguments filed 5/20/02 have been fully considered but they are not persuasive. With respect to the objection to the specification, Applicant has argued that the format suggested by the Examiner is merely a "guideline" that is "suggested" in the MPEP for Applicant's use. The proposed format is not required by statute or PTO rules. Accordingly, Applicant submits that amendment is not necessary as the present specification already is

understandable to the skilled artisan and conforms to all formality requirements of the PTO rules is unpersuasive. Although, the propped format is not required by statute as indicated by Applicant, however, MPEP 608.01(a) clearly states that the following guidelines, illustrate the preferred layout and content for patent applications. This guidelines are suggested for the applicant's use.

(a) Title of the Invention.

(b) Cross-References to Related Applications.

© Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).

(e) Background of the Invention.

1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(I) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821-1.825).

Further, current PTO practice clearly requires for the specification to have Headings as required by MPEP 608.01(a) which states that the text of the specification sections defined in paragraphs (a) through (l) as shown above, if applicable, should be preceded by a section heading in uppercase and without underling or bold type. Thus, the specification is again is objected because there are no headings disclosed in the disclosure as required by PTO practice and MPEP 608.01(a).

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The rejection of claims 24-51 under 35 U.S.C. 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed. Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657).

Applicant asserts that in the attached manufacturer's catalogue, Factor VIII (FVIII) , which has a molecular weight of about 300 kd, is shown as not being able to pass through the Planova 15N filter. In theory, only molecules having a molecular weight below 160 kd can pass through a 15 nm filter. Surprisingly, the inventors have found that FVIII is able to pass through this filter most likely because of its shape and flexibility. Accordingly, the process of the present invention not only purifies FVIII from other plasma proteins but also filters viruses because viruses cannot pass through the 15 nm filter. This is unexpected result, not taught or suggested by the prior art is noted. However, contrary to Applicant's assertion, the combined teachings of the prior art employ a method for obtaining a virus free solution of the plasma protein complex of

FVIII, said solution essentially being free of high molecular weight vWF and obtained from a solution containing high molecular weight FVIII-vWF complexes, said method combining a dissociation step and a filtration step using a filter with a porosity of 15 nm.

Thus, for Applicant to validate the unexpected result as asserted above, Applicant has to show a side by side comparison with unexpected results showing that there is a patentable difference between the instant invention's method of purification or filtration of FVIII solution and the prior art method of purification or filtration of FVIII solution. However, Applicant is cautioned that this is not an invitation to prolong the prosecution of after Final rejection.

Furthermore, a proper *prima facie* case of obviousness is overcome by evidence that the prior art teaches away from the invention, or by evidence that the claimed invention yields unexpected superior results. Applicant has not presented rebuttal evidence in order to prevail the *prima facie* obviousness presented by the Examiner. Hence, the rejection under 35 U.S.C. 103(a) over the prior art of record is maintained for the same reasons discussed on the previous Office action as reiterated below:

WO 96/00237 teaches a method of virus-filtering a solution that contains at least one macromolecule, particularly factor VIII which may be native or recombinant, wherein the salt content of the solution lies in the range of from about 0.2 M up to saturation of the solution with the salt concerned (See e.g., abstract, page 5, lines 14 to 24 and claim 1). On page 7, lines 30 to page 9, lines 27, the reference clearly teaches the use of various filters which are readily available commercially such as Planova™ 15 filter for virus filtration having a porosity as low as 15 nm

for the intended purpose of reducing the content of very small non-enveloped viruses, such as parvoviruse, polio virus, hepatitis virus, ect. Thus, the primary reference clearly teaches a method for obtaining a variety of safe solution of the plasma protein complex such as FVIII by a filtration step using a filter with a porosity of 15 nm.

The primary reference of WO 96/00237 differs from claims 24-51 in not using chaotropic ions such as calcium for dissociation purpose and the purification of the cryoprecipitate fraction of the plasma by ion exchange chromatography. However, Josic et al. teach the purification of FVIII and vWF from human plasma by anion-exchange chromatography, wherein the purification is carried out by a combination of precipitation and chromatographic procedures. After precipitation, the first step in virus inactivation is achieved through the effect of a non-ionic detergent such as Tween 80, and as solvent such as TnBp (i.e., inactivated by solvent/detergent treatment as claimed in claim 41). By anion-exchange chromatography, a highly enriched product consisting of a complex formed by FVIII and vWF is isolated. The second step in virus inactivation is conducted with the addition of stabilizers, pasteurization and subsequent removal by ion-exchange chromatography. The resulting complex of FVIII and vWF are dissociated by adding calcium ions and subsequently both glycoproteins from the complex are separated from one another by further anion-exchange chromatography (See e.g. abstract, pages 183-184 and Figure 1). Thus, clearly teaching the separation of FVIII and vWF using treatment by calcium ions after purification of the FVIII-vWF plasma complex using chromatographic techniques.

Further, Grandgeorge et al (U.S. Patent No. 5,71,195) teaches a method for purifying FVIII from cryoprecipitate, enabling chromatographic yields of more than 90% to be achieved by dissolving FVIII and subjecting to viral inactivation with solvent/detergent and further subjecting to chromatography on a weak anion-exchange column which is hydrophilic in nature and FVIII is then eluted with a dissociating buffer (See e.g. abstract and summary of the invention). Furthermore, Farb et al discloses a multi-step process for separating FVIII from plasma in which at least one of the steps require the adsorption of FVIII on a hydrophilic interaction matrix (See e.g. summary of the invention). Moreover, as acknowledged on page 2, lines 23-32 in the instant specification, the elimination of vWF proteins (that is, implicitly, high molecular weight vWF, and therefore, implicitly, free of high molecular weight vWF). Thus in view of this and in view of the teachings of the secondary references, one of ordinary skill in the art could have envisaged filtering the solution of dissociated FVIII/vWF which is obtained as a product which is free of virus and devoid of vWF by combining a filtration and dissociation steps using a filter with a porosity of 15 nm. Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary references to the primary reference because such features are known or suggested in the art, as seen in the secondary references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claim 51, the claim is in product-by-process format and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the

recited process steps, In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, In re Best, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to the Applicants, In re Fitzgerald, 205 USPQ 594.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ a method for obtaining a virus free solution of the plasma protein complex of FVIII, said solution essentially being free of high molecular weight vWF and obtained from a solution containing high molecular weight FVIII-vWF complexes, said method combining a dissociation step and a filtration step using a filter with a porosity of 15 nm., absence of sufficient objective factual evidence or unexpected results to the contrary.

The following is a new ground of rejection necessitated by Applicant's amendment.

CLAIMS REJECTION-35 U.S.C. § 112 [2nd] PARAGRAPH

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 24 is indefinite and confusing in the recitation "essentially free of viruses" and "essentially devoid of vWF and factor VIII-vWF complexes" because the term "essentially" is a relative term, and as such, the metes and bounds of the claim can not be determined from the claim language. Thus, the solution is either free from the viruses or not. Similarly, the solution is either free of vWF and FVIII-vWF or not. Appropriate clarification is required.

Claim 31 is indefinite in the recitation "....a $CaCl_2$ solution, 0.35 M to saturation" because it is not clear if 0.35 M refers to $CaCl_2$ solution. It appears to be typographical error. Appropriate correction is suggested.

Claim 38 recites the limitation "wherein the starting factor VIII fraction" in line 1. There is insufficient antecedent basis for this limitation in claim 24 or claim 36 or claim 38.

Claim 41 is indefinite in the recitation "an anti-viral solvent and/or detergent" because it contains the use of an alternative expression wherein the limitation covers two elements, i.e., "solvent" is not the same as "detergent" and vise versa.

Claims 46 and 47 recite the limitation "wherein the concentration C" in line 1. There is insufficient antecedent basis for this limitation in claim 24 or claim 46 or claim 47, respectively.

Claims 47-49 are indefinite and vague in the recitation "....from approximately 10 to approximately 50 U/ml" (claim 47), "...from approximately 0.05 to approximately 0.5 mg/ml" (claim 48) and ".....from approximately 0.1 to approximately 0.5 mg/ml" (claim 49), respectively

because the term "from approximately" does not give a definite range. Amendment of the claims to recite "approximately.....to approximately.....: is suggested.

Claims 48 and 49 recite the limitation "wherein the protein content" in line 1. There is insufficient antecedent basis for this limitation in claim 24 or claim 48 or claim 49, respectively.

ACTION IS FINAL, NECESSITATED BY AMENDMENT

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m.. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Mohamed/AAM

July 26, 2002